Vaccines and Related Biological Products Advisory Committee Meeting

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FDA Briefing Document

HEPLISAV (Hepatitis B Vaccine Recombinant and 1018 ISS Adjuvant)

Applicant:

Dynavax Technologies Corporation

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1.0 General Information

1.1 Product: HEPLISAV (rHBsAg-1018 ISS)

- Recombinant Hepatitis B surface antigen (rHBsAg), subtype *adw*, produced in yeast cells (*Hansenula polymorpha*).
- Combined with a novel cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant.
- 1018 ISS used in HEPLISAV is a 22-mer oligonucleotide with the sequence:

5' TGA CTG TGA ACG TTC GAG ATG A 3'

1.2 Proposed Indication: Active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age.

1.3 Dosage and Administration: Each 0.5mL dose contains 20 mcg rHBsAg and 3000 mcg 1018 ISS adjuvant. The dosing regimen is two 0.5 mL doses administered 1 month apart.

2.0 Executive Summary

HEPLISAV was evaluated in two pivotal phase 3 immunogenicity and safety studies (DV2-HBV-10 and -16; N=3789 HEPLISAV recipients), three supportive immunogenicity studies and seven supportive safety studies. Immunogenicity of HEPLISAV was assessed by determining the seroprotection rate (SPR): the proportion of subjects with an anti-HBsAg level ≥ 10 mIU/mL, an antibody concentration recognized as conferring protection against hepatitis B virus infection (1, 2). Study DV2-HBV-10 enrolled adolescents and adults 11-55 years of age; Study DV2-HBV-16 enrolled adults 40-70 years of age. In both pivotal studies, the SPR following two doses of HEPLISAV was non-inferior to the SPR induced by three doses of the licensed hepatitis B vaccine Engerix-B (GlaxoSmithKline; GSK). At least 90% of healthy adult subjects maintained seroprotective antibody levels against hepatitis B at 48 weeks after two doses of HEPLISAV in Study DV2-HBV-16. Subgroup analyses did not reveal clinically significant differences between antibody responses in younger and older subjects, or between males and females. Conclusions could not be drawn regarding differences among ethnic and racial subgroups, though the SPRs were similar among all ethnic groups examined.

Safety was evaluated in 5845 subjects (HEPLISAV n=4425, Engerix-B n=1420) 18 years of age and older enrolled in nine clinical trials: 2 pivotal studies, DV2-HBV-10 and DV2-HBV-16 and 7 supportive studies. The safety evaluation comprised an assessment of local and systemic reactogenicity monitored for days 0-6 after vaccination in both pivotal studies, unsolicited adverse events (AEs) and serious adverse events (SAEs) monitored through week 28 in Study DV2-HBV-10. In Study DV2-HBV-16, unsolicited AEs were monitored through week 28 and SAEs and autoimmune events were monitored through week 52. Anti-dsDNA and anti-nuclear antibody (ANA) levels were measured in both pivotal studies. Anti-neutrophil cytoplasmic antibody (ANCA) levels were measured in Study DV2-HBV-16.

Most AEs were related to local reactogenicity, were described as mild in intensity, and did not differ significantly from the licensed comparator, Engerix-B. One case each of vasculitis in the HEPLISAV treatment arm (cyotoplasmic-ANCA [c-ANCA] positive Wegener's granulomatosis) and Engerix-B treatment arm (perinuclear-ANCA [p-ANCA] positive vasculitis) and one case of Guillain-Barre syndrome in the HEPLISAV arm, were identified in pivotal study DV2-HBV-10 which prompted a closer examination for autoimmune adverse events in Study DV2-HBV-16. The overall safety evaluation across studies did not reveal significant imbalances in rates of clinically important adverse events. No significant differences in ANA titers, ANCA or anti-dsDNA levels were detected between recipients of HEPLISAV or Engerix-B. Subgroup analysis for AEs did not identify subgroups of subjects that exhibited higher rates of AEs than other groups. The CBER clinical reviewers concluded that analyses of the two pivotal studies and the integrated summary of safety did not reveal any clinically significant differences in safety between HEPLISAV and its active comparator, Engerix-B. The safety database for HEPLISAV may not have sufficient power to detect rare adverse events.

3.0 Introduction and Background

3.1 Epidemiology

Hepatitis B infects more than 2 billion persons worldwide, and 350-400 million persons are chronic carriers. Each year chronic HBV causes 0.5 to 1.0 million deaths from end-stage liver disease and hepatocellular carcinoma. In the U.S., universal childhood vaccination has been recommended since 1992. Subsequently, the incidence of HBV infection has substantially decreased from 8.5 per 100,000 (1990) to 1.6 per 100,000 (2006). Prevalence remains high at 800,000 to 1.4 million, and chronic HBV infection causes 2,000-4,000 deaths annually. CDC estimated that there were 38,000 new HBV infections in 2009 with 43% occurring in adults over 40 years of age. Forty-seven to 70% of U.S. residents with chronic HBV infection were born in other countries.

Transmission of HBV is by percutaneous and mucosal exposure to infectious blood or body fluids. In the U.S. transmission is primarily sexual. Injection drug use (IDU) accounts for 16% of new HBV infections. Nosocomial transmission between patients and from patients to health care workers (HCW), including hemodialysis (HD) and oncology units, has become rare, declining 95% since implementation of routine vaccination and standard precautions for blood-borne pathogens. The incidence of HBV infection among hemodialysis patients was 1.2% in 2002.

3.2 Currently Available Interventions

Two licensed vaccines, both made from yeast-derived recombinant antigen adsorbed to aluminum compounds are currently available for the prevention of HBV in the U.S., Engerix-B (GSK) and Recombivax HB (Merck). There is also one combination vaccine for adults, Twinrix (GSK), which includes a hepatitis A vaccine component. Engerix-B and Recombivax HB are both approved for use in adults and adolescents as a three-dose series to be administered at months 0, 1 to 2, and 6 to 12. A two-dose Recombivax HB series, administered at 0, and 4 to 6 months, is also approved for adolescents 11 to 15 years of age. Additionally an accelerated schedule is licensed for Twinrix—a series of four doses (1 mL each), given on Days 0, 7 and Days 21 to 30, followed by a booster dose at Month 12.

These vaccines are highly effective, as shown in controlled clinical trials of efficacy against acute hepatitis B infection (1) and prospective observational studies (2, 3), and elicit a SPR in approximately 95% of healthy adults. Long-term studies of immunocompetent adults and children indicate that immune memory remains intact for up to two decades and protects against symptomatic acute and chronic HBV infection, even though anti-HBs antibody concentrations may become low or undetectable over time (3).

Breakthrough infections (detected by presence of anti-HBc antibodies or HBV DNA) have occurred in immunized people, but these infections typically are transient and asymptomatic. Chronic HBV infection in immunized people has been documented in dialysis patients whose anti-HBsAg antibody concentrations fell below 10 mIU/mL. For adults on dialysis, formulations of Engerix-B and Recombivax HB containing 40 mcg per dose administered in a 3 or 4 dose series are approved. In dialysis patients, the need for booster doses is assessed by annual antibody testing, and revaccination is indicated when anti-HBsAg levels decline below 10 mIU/mL.

3.3 Mechanism of Action of 1018 ISS Adjuvant

HEPLISAV consists of rHBsAg and a synthetic cytosine phosphoguanine oligodeoxynucleotide (CpG ODN) adjuvant, 1018 ISS, which is comprised of cytosine and guanine enriched unmethylated single strand DNA sequences. There is currently no other licensed vaccine in the U.S. that contains this adjuvant. The mode of action of CpG ODNs is based on the concept that, whereas vertebral (self) DNA is usually methylated when a cytosine is followed by a guanine, bacterial and viral DNA contain unmethylated CpG sequences, which are recognized as foreign by the innate immune system through interaction with toll-like receptor 9 (TLR9).

TLR9 receptors are located within the cytoplasm of plasmacytoid dendritic cells (pDCs) and B cells, on the surface of the endoplasmic reticulum (ER). They are present to a lesser degree in NK cells. Activation of antigen-presenting pDCs and B-cells occurs when intracellular viral and bacterial pathogens containing unmethylated CpG sequences are recognized by TLR9 receptors. Activated pDCs become antigen presenting cells (APCs) and secrete interferon-alpha (IFN-α), which in turn stimulates a T helper 1 (Th1) immune response, and the secretion of other proinflammatory cytokines that activate macrophages, monocytes, and NK cells. Activated B-cells are stimulated to secrete antibodies, nonspecifically autoantibodies, and contribute to the overall biased Th1 cellular immune response by facilitating opsonization and antibody-dependent cytotoxic T cell responses.

The 1018 ISS adjuvant in HEPLISAV is thought to have the following effects: (1) activation of pDCs through TLR9, (2) conversion of pDCs into activated dendritic cells that present the processed HBsAg component of HEPLISAV to CD4+ T cells, and (3) promotion of Th1 T-cell differentiation through the production of IFN-α and IL-12. This activation is thought to result in a high and sustained antibody response, likely due to generation of large numbers of anti-HBsAg-secreting plasmacytes and HBsAg-specific memory cells.

In summary, HEPLISAV is proposed to act by using an adjuvant that activates TLR9 in pDCs which combined with HBsAg, leads to production of HBsAg-specific antibodies.

3.4 TLR Activation and the Potential for Autoimmunity

While TLR activation is critical for initiation of the innate and adaptive immune response to invading pathogens, the inappropriate activation of the innate immune system may induce autoimmune responses and chronic inflammatory diseases (16-18). While rare, vasculitis, particularly polyarteritis nodosa, has been associated with natural hepatitis B infection (4). Immunizations with hepatitis B virus, with or without CpG, also may be associated with autoimmune disease in otherwise healthy individuals (19-21), though a recent Institute of Medicine review did not find any causal relationship between hepatitis B vaccination and autoimmune diseases (4). The difficulty in defining the potential role of vaccines and/or adjuvants in the development of autoimmune disease is in part due to the multifactorial nature of autoimmunity, and in part due to the apparent heterogeneity and scope of potential contributing factors. In light of the theoretical potential for TLR-agonist adjuvants, such as CpG, to induce or exacerbate autoimmune disease in humans, efforts were made to identify clinical cases of autoimmunity and evaluate biomarkers of autoimmunity, such as anti-dsDNA, ANA, and ANCA, in individuals enrolled in studies of HEPLISAV.

3.5 Non-Clinical Data on 1018 ISS Adjuvant

Non-clinical toxicology studies were conducted with HEPLISAV or 1018 ISS alone in a number of rodent and non-human primate (NHP) studies.

Tissue distribution studies in mice revealed highest concentrations in kidney, liver, lymph node, and spleen. The primary mode of clearance is by degradation (exonuclease activity) in tissues and is slow because the phosphorothioate backbone resists degradation. Renal clearance is low and elimination from tissues is slow.

In a single dose mouse study of HEPLISAV, no mortality or clinical toxicity was seen, with mild anemia and associated mild extramedullary hematopoiesis noted. There was no assessment of anti-DNA antibodies. In a two-dose mouse study of HEPLISAV, 43- and 67-fold clinical multiples of vaccine dose failed to induce anti-dsDNA. In a rat study of 1018 ISS alone, 11 to 272-fold clinical multiples of a vaccine dose resulted in thrombocytopenia, anemia, lymphocytosis, neutrophilia, and monocytosis. Elevated BUN, renal tubular degeneration, interstitial inflammation and oligonucleotide deposition in the renal proximal tubular epithelial cells was seen, but no effect on renal function, and no specific findings of glomerulonephritis or vasculitis were detected. Non-clinical investigations of the potential for CpGs or HEPLISAV to induce autoimmunity have been suboptimal given the lack of an appropriate mouse or well-characterized NHP models of human autoimmunity.

3.6 Relevant Prior Human Experience

Limited prior human experience exists for the adjuvant 1018 ISS. More clinical experience is available with CpG 7909 (ProMune, Coley Pharmaceuticals), another immunostimulatory synthetic cytosine phosphoguanine oligonucleotide (ODN) agonist of TLR9, in the context of use in the cancer patient population. These studies (25+) have

been difficult to interpret due to the heterogeneous population of cancer patients (n ~ 2000) receiving various vaccines and antigenic tumor peptides, some with chemotherapy and other immunomodulators. A summary of autoimmune events for CpG 7909 from reports in the literature did not reveal autoimmune signals. Seroconversions occurred in anti-dsDNA (25%), ANA (10%), rheumatoid factor (RF, 7%), and anti-thyroid antibody (3.5%), but without clinical evidence of autoimmune disease.

CpG 7909 has been administered with Engerix-B in a double-blind phase 1/2 study in healthy subjects 18-35 years of age (24). The most frequently reported adverse events were injection site reactions, flu-like symptoms and headache. Autoimmune adverse events were not reported. A second, similar study performed in thirty-eight HIV-infected individuals 18-55 years of age (25) failed to reveal any autoimmune adverse events, although transient elevations above normal range for anti-dsDNA were noted in two subjects who received Engerix-B plus CpG 7909 and in two subjects who received CpG 7909 alone. These subjects were ANA negative.

3.7 Dose Selection of 1018 ISS Adjuvant

The rationale for dose selection of 1018 ISS for further clinical development and for the candidate vaccine formulation was based on results from the pilot Study DV2-HBV0001. This was a phase 1, observer-blind, randomized, dose-escalation study performed in healthy, seronegative adults 18-55 years of age, that evaluated the safety, tolerability and immune response to rHBsAg, 20 micrograms (mcg), co-administered by intramuscular injection (IM) with differing doses of 1018 ISS. Doses of 1018 ISS administered were 300, 650, 1000, or 3000 mcg.

Two IM doses of rHBsAg, 20 mcg, combined with the highest dose of 1018 ISS evaluated in this study (3000 mcg) yielded the highest seroprotection rate, based on the limited seroprotective response data presented.

4.0 Overview of Clinical Studies

Studies comprising the immunogenicity and safety analysis are presented in Table 1:

Table 1: Summary of Completed Studies of HEPLISAV

	Study Design	HEPLISAV Dose/Schedule/N	Active Comparator Dose/Schedule/N	Key Immunogenicity Endpoint(s)
Pivotal Studies				
HBV-10	Phase 3, observer-blind, randomized, active-controlled, parallel group, multi-center study in healthy subjects 11-55 years of age conducted in Canada and Germany	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1820	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks N=608	Primary Endpoint: SPR at Week 12 for HEPLISAV and Week 28 for Engerix-B
HBV-16	Phase 3, observer-blind, randomized, active-controlled, parallel group, multi-center study in healthy adult subjects 40-70 years of age conducted in Canada and Germany	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1969	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks N=483	Primary Endpoint: SPR at Week 12 for HEPLISAV and Week 32 for Engerix-B Lot consistency of HEPLISAV measured by GMC at Week 8
Supportive Studies				
HBV0001	Phase 1 Observer-blind, randomized, dose-escalation study of the 1018 ISS Adjuvant component of vaccine in healthy, seronegative adults 18-55 years of age conducted in Canada.	1018 ISS Adjuvant: 300 mcg, ± 20 mcg HBsAg 650 mcg, ± 20 mcg HBsAg 1000 mcg, ± 20 mcg HBsAg 3000 mcg, ± 20 mcg HBsAg Schedule: 0, 8 weeks IM N=32	HBsAg: 20 mcg N=8 1018 ISS Adjuvant Alone: 300, 650, 1000, 3000 mcg N=8	Anti-HBsAg GMC measured after vaccination
HBV-02	Phase 2 Observer-blind, randomized, parallel group study of hypo- and non-responders to licensed hepatitis vaccine in adults 18-65 years of age conducted in Canada	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: Single injection IM N=30	Engerix-B: 20 mcg HBsAg Schedule: Single injection IM N=29	SPR at Week 4
HBV-03	Phase 2 Observer-blind, randomized, parallel-group study in adults 18-28 years of age conducted in Canada.	HEPLISAV: 20 mcg HBsAg/ 3000 mcg 1018 ISS adjuvant Schedule: 0, 8 weeks IM (placebo/meningococcal vaccine at 24 weeks) N=48	Engerix-B: 20 mcg HBsAg Schedule: 0, 8, 24 weeks IM N=51	SPR at Week 28

SPR: Seroprotection Rate: anti-HbsAg level ≥ 10 mIU/mL

Source: *BLA STN 125428, Summary of Clinical Efficacy, Table 2.7.3-2, page 14 of 77*

5.0 Pivotal Clinical Immunogenicity and Safety Studies Conducted with HEPLISAV

5.1 Study DV2-HBV-10: A Phase 3 Safety and "Efficacy" Study to Compare Immune Responses following Injection with Either Two Doses of HEPLISAV or Three Doses of Engerix-B

5.1.1 Study Design

This phase 3 study was a subject and observer-blind, randomized, controlled study of approximately 2400 subjects, 11-55 years of age (ages 18-55 in Germany) conducted at 21 sites in Canada and Germany. Subjects were randomized 3:1 to receive either HEPLISAV or Engerix-B vaccine. Enrollment of subjects was stratified by age (11 to 39 years of age and 40 to 55 years of age). Subjects randomized to Engerix-B received three 1.0 mL (20 mcg) injections of Engerix-B, the FDA-approved dose for adults not on dialysis. Subjects randomized to HEPLISAV received two injections of HEPLISAV vaccine at Weeks 0 and 4 and saline placebo at Week 24. Thus, all subjects received a total of three injections (active vaccine or matching placebo), given on Day 0, Week 4, and Week 24. The duration of the study was 28 weeks.

5.1.2 Study Objectives

The primary immunogenicity objective was to compare the proportion of subjects who exhibit seroprotective antibody levels at Week 12 following vaccination with HEPLISAV at 0 and 1 month to the proportion of subjects who exhibit seroprotective antibody levels when measured at Week 28 following vaccination with the active comparator, Engerix-B, at 0, 1, and 6 months. The primary safety objective of this study was to demonstrate safety and tolerability of vaccination with HEPLISAV when administered to adolescent and adult subjects.

5.1.3 Study Population

The study population comprised HBV seronegative male and female subjects 11-55 years of age who were serum negative for HBsAg (defined as an anti-HsBAg antibody level < 5 mIU/mL), anti-HBsAg antibody and anti-HBcAg antibody and who had never received any prior HBV vaccine (one or more doses). Subjects who were at high risk for recent exposure to HBV, HCV or HIV (e.g., current intravenous (IV) drug use, unprotected sex with known HBV, HCV or HIV positive partner) were excluded from the study.

5.1.4 Endpoints and Criteria for Study Success

The primary immunogenicity endpoint was the SPR after the final active injection. The primary immunogenicity analysis determined the difference in SPR between the Engerix-B group at Week 28 and HEPLISAV group at Week 12. If the upper limit of the 2-sided 95% CI was below the pre-specified non-inferiority criterion of +10%, HEPLISAV was determined to be non-inferior to Engerix-B.

The secondary immunogenicity endpoint was the SPR at Week 4, which was measured 4 weeks after the first injection (onset of response) for both treatment groups.

An exploratory analysis evaluated the SPR for HEPLISAV vs. Engerix-B at all other serology time points (Weeks 8, 12, 24, and 28).

A summary table of immunogenicity testing and description of primary, secondary, and exploratory endpoints is presented in Table 2:

Table 2: Immunogenicity Testing (Study DV2-HBV-10)

Hypothesis	HEPLISAV Time points (weeks)	Engerix-B Time points (weeks)	Study Parameter
Primary	12	28	SPR
Secondary	4	4	SPR
Exploratory	8, 12, 24, 28	8, 12, 24, 28	SPR
Exploratory	8	28	SPR
Exploratory	4, 8, 12, 24, 28	4, 8, 12, 24, 28	GMT

HEPLISAV administered at weeks 0 and 4.
Engerix-B administered at weeks 0, 4, and 24.
Source: *BLA 125428, DV2-HBV-10, Statistical Analysis Plan, Table 1, Page 12 of 30*

5.1.5 Populations Analyzed

Two populations were considered for the immunogenicity analysis:

1. The Per-Protocol Population: defined as subjects who met the eligibility criteria, did not violate the protocol in a substantial manner, received all protocol-specified study injections, had anti-HBsAg measurements and all injections within the specified day ranges, and had an anti-HBsAg measurement at the time defined by the protocol. This population was used for the primary immunogenicity analysis.
2. The modified intent-to-treat (ITT) Population: defined as subjects who received at least one study injection and had at least one post-baseline anti-HBsAg level.

Safety was evaluated using the 'safety population', defined as enrolled subjects who received at least one study injection and had any post-baseline safety data. Subjects were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data. All 2415 enrolled subjects were included in the safety analysis population (n=1809 in HEPLISAV and n=609 in the Engerix-B groups).

5.1.6 Subject Disposition

A total of 2910 subjects were screened for this study and 2428 enrolled. Thirteen subjects (0.5%) were adolescents (< 18 years), of whom 11 were assigned to the HEPLISAV group and 2 subjects were assigned to Engerix-B. The remaining 2415 subjects were adults, including 1809 subjects assigned to HEPLISAV and 606 subjects assigned to Engerix-B. Although this phase 3 study was originally designed to evaluate safety and immunogenicity in subjects aged 11 to 55 years, only 13 (0.5%) of the 2428 subjects enrolled in the study were younger than 18 years. Accordingly, the results of this study focused on adult subjects only (18 through 55 years).

Approximately 97% of all adult subjects completed the study. The most common reason for subject discontinuation was 'lost to follow-up', reported by 1.7% of subjects in each group. Additional reported reasons for discontinuation were adverse events (AEs), subject noncompliance, and subject withdrawal of consent.

5.1.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics were similar between the two treatment groups, with no statistically significant differences found. Within each group, almost all subjects were white or non-Hispanic/Latino, the mean age was approximately 40 years, and the percentage of females was slightly higher than that of males. More than 99% of subjects in each treatment group had an anti-HBsAg level below 5 mIU/mL at baseline. The majority of enrolled study subjects (63-64% for both treatment groups) were non-smokers.

5.1.8 Immunogenicity Results

Primary Immunogenicity Endpoint

The estimated difference in SPR between the Engerix-B and HEPLISAV groups and associated 95% CI was -13.9% (CI: -17.6, -10.6). The upper limit of the CI was -10.6%, which was below the pre-specified non-inferiority criterion of +10%, establishing that the SPR at the Week 12 time point for HEPLISAV was non-inferior to that of Engerix-B at Week 28, thereby meeting the pre-specified criterion for non-inferiority (Table 3).

Immunogenicity analysis of the primary endpoint was also performed for the mITT population and was found to be consistent with that of the per protocol population (data not shown).

Table 3: Primary Immunogenicity Endpoint Analysis (Study DV2-HBV-10): SPR for HEPLISAV (Week 12) compared with Engerix-B (Week 28): Per-Protocol Analysis Population, Adults 18-55 Years of Age

HEPLISAV[a] SPR (%) (n/N)	Engerix-B[b] SPR (%) (n/N)	Estimated Difference in SPR[c] (Engerix-B – HEPLISAV (95%) CI)	Non-inferiority Criteria Met?[d] (Yes/No)
95.04 % (12 weeks) (1479/1556)	81.13 % (28 weeks) (432/533)	-13.91 (-17.59, -10.61)	Yes

CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.
[a] Study injections were given at Weeks 0, 4, 24 (placebo). [b] Study injections were given at Weeks 0, 4, 24.
[c] Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years). [d] Non-inferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).
Source: *BLA STN 125428, Clinical Study Report, HBV-DV2-10, Section 11.1.1, Table 11-1, page 63 of 204*

Secondary Immunogenicity Endpoint

The secondary immunogenicity endpoint was the SPR at Week 4 (i.e., 4 weeks after dose 1) for both the HEPLISAV and Engerix-B in the 'per protocol' adult population (age 18-55 years). The SPRs at this time point were 23.63% for HEPLISAV and 3.98% for Engerix-B, respectively. The estimated difference between the SPR for Engerix-B and HEPLISAV groups and associated 95% CI was -19.66% (CI: -22.37, -16.80). Because the upper limit of the CI was -16.8, which was below the pre-specified non-inferiority

criterion of +10%, the immune response at the Week 4 time point for HEPLISAV was found to be non-inferior to that of Engerix-B (Table 4).

Table 4: Secondary Immunogenicity Endpoint Analysis (Study DV2-HBV-10): SPR at Week 4 for HEPLISAV compared with Engerix-B; Per-Protocol Analysis Population, Adults 18-55 Years of Age

Visit	HEPLISAV[a] SPR (%) n, N	Engerix-B[b] SPR (%) n, N	Estimated Difference in SPR[c] (Engerix-B – HEPLISAV (95%) CI)	Non-inferiority Criteria Met?[d] (Yes/No)
Week 4	23.63 % 366, 1547	3.98 % 21, 531	-19.66 (-22.37, -16.80)	Yes

CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).[b] Study injections were given at Weeks 0, 4, 24.
[c] Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years).
[d] Non-inferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).
Source: *BLA STN 125428, DV2-HBV-10, Clinical Study Report, Table 11-2, page 64 of 204*

Exploratory Endpoints

Exploratory endpoints to evaluate the kinetics of the immune response included the SPRs at Weeks 8, 12, 24, and 28 and the anti-HBsAg GMC at Weeks 4, 8, 12, 24, and 28 for both treatment groups as well as the SPR at 4 weeks after the final active injection (Week 8 for HEPLISAV and Week 28 for Engerix-B). These were studied to evaluate the kinetics of vaccination on the immune response. Results of these analyses are provided in Table 5 and 6.

Table 5: Exploratory Endpoints (Study DV2-HBV-10): SPR at Weeks 8, 12, 24, and 28 for HEPLISAV compared with Engerix-B: Per-Protocol Analysis Population, Adults 18-55 Years of Age

Visit	HEPLISAV[a] SPR (%) (n/N)	Engerix-B[b] SPR (%) (n/N)	Estimated Difference in SPR[c] (Engerix-B – HEPLISAV (95% CI)
Week 8	88.54 % (1372/1549)	26.46 % (140/531)	-62.08 (-65.96, -57.89)
Week 12	95.04% (1479/1556)	22.59% (120/533)	-72.45 (-75.95, -68.57)
Week 24	98.25% (1521/1548)	32.49% (172/531)	-65.76 (-69.66, -61.60)
Week 28	97.94% (1524/1556)	81.13% (432/533)	-16.81 (-20.42, -13.60)

CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.
[a] Study injections were given at Weeks 0, 4, 24 (placebo).[b] Study injections were given at Weeks 0, 4, 24.
[c] Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years). The Miettinen and Nurminen method was used to calculate the 95% confidence intervals.
Source: *BLA STN 125428, DV2-HBV-10, Clinical Study Report, Table 11-3, page 67 of 204*

Anti-HBs Ag GMCs are presented in Table 6. At Week 28, the Engerix-B GMC levels were shown to be slightly higher (348.17 mIU/mL) than that of HEPLISAV (319.98 mIU/mL).

Table 6: Exploratory Endpoints (Study DV2-HBV-10) Serum Anti-HBsAg Antibody Geometric Mean Concentration by Visit: Per-Protocol Analysis Population, Adults 18-55 Years of Age

Visit	HEPLISAV (N=1557)* GMC (mIU/mL), 95%CI	Engerix-B (N=533) GMC (mIU/mL), 95%CI
Week 4	5.50 (5.13, 5.88)	2.92 (2.75, 3.11)
Week 8	81.51 (75.08, 88.50)	6.44 (5.61, 7.39)
Week 12	136.86 (127.50, 146.80)	5.48 (4.85, 6.19)
Week 24	342.54 (320.15, 366.51)	7.19 (6.31, 8.20)
Week 28	319.98 (298.23, 343.30)	348.17 (265.92, 455.87)

* N= Number of subjects in the analysis population in the treatment group.
Non-missing anti-HBsAg results reported as < 5 mIU/mL were considered as 2.5 mIU/mL.
HEPLISAV administered at weeks 0 and 4. Engerix-B administered at weeks 0, 4, and 24.
Source: *BLA STN 125428, DV2-HBV-10, Clinical Study Report, Table 11-4, page 67 of 204*

Immunogenicity Conclusion: Based on the primary immunogenicity endpoint data, HEPLISAV met the pre-specified non-inferiority criteria for immunogenicity as compared to the licensed active comparator hepatitis B vaccine, Engerix-B.

5.1.9 Safety Results (Study DV2-HBV-10)

Safety and tolerability were evaluated until Week 28 on the basis of the following parameters: solicited post-injection local and systemic AEs, unsolicited AEs, SAEs, clinical laboratory results, including ANA and anti-dsDNA, and oral temperature. Descriptive statistical analyses (count and percentage) were provided for all clinical parameters. Solicited systemic and local AEs (days 0-6), systemic AEs and treatment related local AEs occurring in ≥1% of subjects in any group (days 0-28) and temperature elevations ≥ 100.4 degrees Fahrenheit (day 0-6) were provided. ANA and anti-dsDNA were measured at baseline and at Week 28.

Solicited adverse events included local pain, redness and swelling, fatigue, headache malaise and oral temperature and were recorded and rated by severity by the subjects on diary cards from Week 0 through Week 28. These data are presented in Table 7.

Table 7: Summary of Solicited Local Reactions (Days 0-6) Following Each Injection for Subjects ≥ 18 Years Old (Study DV2-HBV-10)

	Week 0 (Dose 1)	Week 0 (Dose 1)	Week 4 (Dose 2)	Week 4 (Dose 2)	Week 24 (Dose 3)	Week 24 (Dose 3)
	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	Placebo N=1809 n (%)	Engerix-B N=606 n (%)
n	1809 (100)	606 (100)	1797 (99.3)	604 (99.7)	1768 (97.7)	598 (98.7)
Pain, n (%)	697 (38.5)	203 (33.5)	624 (34.7)	150 (24.8)	109 (6.2)	121 (20.2)
Redness[1] n (%)	75 (4.1)	3 (0.5)	53 (2.9)	6 (1.0)	5 (0.3)	4 (0.7)
Swelling[1] n (%)	41 (2.3)	4 (0.7)	27 (1.5)	3 (0.5)	3 (0.2)	3 (0.5)

[1]Redness and swelling events < 2.5cm are not included in the table.
Source: *Adapted from STN 125428, DV2-HBV-10 Clinical Study Report Table 12-4, p. 81*

Overall, more subjects receiving HEPLISAV reported local pain, redness and swelling after the first or second dose than subjects receiving Engerix-B, as shown in Table 8. The majority of events were reported as mild in intensity.

Table 8: Summary of Solicited Systemic Adverse Events (Days 0-6) Following Each Injection for Subjects ≥ 18 Years Old (Study DV2-HBV-10)

	Week 0 (Dose 1)	Week 0 (Dose 1)	Week 4 (Dose 2)	Week 4 (Dose 2)	Week 24 (Dose 3)	Week 24 (Dose 3)
	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	Placebo N=1809 n (%)	Engerix-B N=606 n (%)
n	1809 (100.0)	606 (100.0)	1797 (99.3)	604 (99.7)	1768 (97.7)	598 (98.7)
Fatigue, n (%)	315 (17.4)	101 (16.7)	248 (13.8)	73 (12.1)	139 (7.9)	60 (10.0)
Headache, n (%)	304 (16.8)	117 (19.3)	229 (12.7)	75 (12.1)	159 (9.0)	57 (9.6)
Malaise, n (%)	166 (9.2)	54 (8.9)	137 (7.6)	39 (6.5)	76 (4.3)	38 (6.4)

Source: *Adapted from STN 125428, DV2-HBV-10 Clinical Study Report Table 12-5, p. 83*

For systemic solicited AEs, the incidence and severity of fatigue, headache and malaise were similar between treatment groups. The vast majority of subjects in each treatment arm did not report fever on days 0-6 after each vaccination, and there were no clinically important differences noted in oral temperature between recipients of Heplisav and Engerix B.

Additionally, solicited local and systemic reactions that persisted or worsened past Day 7 were recorded as AEs and included the following:

- Headache (HEPLISAV 11.3%, Engerix-B 10.2%)
- Fatigue (HEPLISAV 1.3%, Engerix-B 0.7%)

The unsolicited adverse events most frequently reported among HEPLISAV recipients are presented in Table 9:

Table 9: Most Frequently Reported Unsolicited AEs among HEPLISAV Recipients (Study DV2-HBV-10)

Adverse Event	HEPLISAV (%)	Engerix-B (%)
Nasopharyngitis	16.8	16.5
Pharyngeal Pain	4.4	4.1
Sinusitis	3.3	2.0
Cough	3.2	2.8
Bronchitis	2.5	2.1
Diarrhea	2.4	2.3
Tooth Disorder	2.2	2.8
Hypertension	2.1	2.8
Upper respiratory infection	1.9	3.1
Abdominal Pain	1.8	2.0
Nausea	1.8	3.3
Gastrointestinal infection	1.7	1.2
Nasal congestion	1.7	0.7
Urinary tract infection	1.6	2.1
Pain in extremity	1.5	1.2

Source: *Adapted from STN 125428, Clinical Study Report: Document Summary Tables, Table 13.1.1A, pages 122-137*

Overall, unsolicited AEs occurred with similar incidence among subjects in each treatment group. A larger proportion of subjects in the Engerix-B arm experienced a severe unsolicited AE (87 [14.4%]) compared to the HEPLISAV arm (192 [10.6%]).

All endocrine disorders reported over the 28 week period of monitoring were thyroid disorders and included the following conditions: hyperthyroidism (HEPLISAV 3 [0.2%], Engerix-B 0), hypothyroidism (HEPLISAV 3 [0.2%], Engerix-B 1 [0.2%], Basedow's disease (HEPLISAV 1 [0.1%], Engerix-B 1 [0.2%], Thyroid disorder (HEPLISAV 1 [0.1%], Engerix-B 0) and Thyroiditis (HEPLISAV 1 [0.1%], Engerix-B 0). One case of Basedow's disease (exophthalmic goiter) in the HEPLISAV arm was graded as severe, all other thyroid disorders were graded as mild or moderate.

Immune system disorders occurred with similar incidence among subjects in each treatment group (HEPLISAV 16 [0.9%], Engerix-B 7 [1.2%]). Musculoskeletal and connective tissue disorders occurred with similar incidence and severity in each group (HEPLISAV total 267 [14.8%], Engerix-B total 85 [14.0%]). One case each of rheumatoid arthritis (HEPLISAV), systemic lupus erythematosis (HEPLISAV), fibromyalgia (Engerix-B) and mixed connective tissue disease (Engerix-B) were diagnosed during the study.

Deaths

No deaths were reported for the 28 week duration of the study.

Serious Adverse Events (SAEs)

All SAEs occurred in subjects 18 years of age and older. Twenty-eight (1.5%) of subjects in the HEPLISAV arm and 13 (2.1%) of subjects in the Engerix-B arm experienced at least one SAE. Overall, the incidence of SAEs was similar between treatment groups and did not raise safety concerns.

Autoimmune Adverse Events

While ANA and anti-dsDNA were evaluated at baseline and Week 28, active surveillance for autoimmune adverse events (AIAEs) was not performed in this study. Based on the occurrence of three AIAEs in this study, the applicant retrospectively analyzed ANCA levels on banked serum. The applicant also implemented active surveillance and independent review of AIAEs prospectively in the subsequent pivotal trial, DV2-HBV-16.

In the HEPLISAV group, two AIAEs occurred: c-ANCA (cytoplasmic ANCA) positive vasculitis (Wegener's granulomatosis) and Guillain-Barre syndrome. In the Engerix-B group, one subject was diagnosed with p-ANCA (perinuclear ANCA) positive vasculitis.

c-ANCA positive vasculitis (Wegener's granulomatosis) (HEPLISAV Group)
A 55-year-old white woman with a medical history of menopause experienced severe widespread urticaria 18 days after the first study injection which was attributed to the consumption of herring. Eleven days after the second study injection, the subject presented with vocal hoarseness. Approximately 8 weeks later, the subject reported symptoms of sinusitis. She reported never having had similar episodes before. She required septal surgery and paranasal sinus drainage. Approximately 7 months after her first vaccination, she was hospitalized for recurrent sinusitis. During this hospitalization she developed a pericardial effusion, pulmonary infiltrates, bilateral pleural effusions and proteinuria. Due to this constellation of symptoms, a serologic workup ensued and an ELISA test was positive for c-ANCA (titer of 1:128, positive for proteinase-3). The c-ANCA test was repeated at two outside reference laboratories with comparable results. A diagnosis of Wegener's granulomatosis was made and she was started on corticosteroids and cyclophosphamide. The subject had both anti-dsDNA and ANA levels within the normal range throughout the study.

The subject's Wegener's granulomatosis was determined by the investigator to be clinically stable 4 months after diagnosis. The investigator assessed the event as serious, severe, and 'possibly related' to study treatment.

Guillain-Barré syndrome (HEPLISAV Group)
A 36-year-old woman with a medical history of splenectomy in 1985 received two study injections and an inactivated influenza vaccine injection 105 days after her second study injection. No complaints or reactogenicity events were noted during this period.

Five days after receiving the influenza vaccine injection, the subject was hospitalized complaining of progressive weakness that progressed to respiratory failure. A diagnosis of Guillain-Barré Syndrome was made. The subject's hospitalization was prolonged by the diagnosis of a follicular variant of papillary carcinoma (thyroid) and bilateral pulmonary embolism. While hospitalized, she was treated with anticoagulants, antibiotics, immunoglobulins, and plasmapheresis, resulting in noticeable improvement.

The subject's Guillain-Barré Syndrome was assessed by the investigator as being severe and 'probably not related' to study treatment but, instead, related to the influenza vaccine the subject received 5 days prior to symptom onset. The subject was discontinued from the study due to the Guillain-Barré Syndrome.

p-ANCA Positive Vasculitis (Engerix-B Group)
A 44-year-old white woman with a medical history that included mixed connective tissue disease and osteoarthritis, experienced fever and approximately 3 months after the 2nd study injection and was treated for presumed pneumonia. She returned to the hospital 127 days following her second study injection with severe dyspnea, hemoptysis, and pleuritic pain. She required intubation and mechanical ventilation. A blood test revealed positive myeloperoxidase-p-ANCA (no titer reported). The subject was then given a provisional diagnosis of p-ANCA associated vasculitis and started on pulse methylprednisolone and cyclophosphamide.

On a further review of the subject's history it was determined that she demonstrated some features of scleroderma but was considered to have a possible crossover syndrome. Further investigation later disclosed a medical history (approximately 10 years prior) of mixed connective tissue disease (MCTD) that was diagnosed and treated with prednisone and chloroquine for over 2 years. She also had pre-existing features of scleroderma. This medical history of MCTD was not disclosed by the subject at the time of study enrollment. A retrospective evaluation of specimens collected at screening revealed that the subject had anti-dsDNA levels within normal range, while her ANA levels were elevated (> 1:5120).

Antinuclear Antibody Assessment
Table 10 outlines the baseline and Week 28 ANA titers for subjects by treatment group and antibody dilution. ANA titers < 1:160 were considered normal.

Table 10: ANA Titers by Treatment Group (Study DV2-HBV-10)

Result	HEPLISAV Baseline N=1809 n (%)	HEPLISAV Week 28 N=1809 n (%)	Engerix-B Baseline N=606 n (%)	Engerix-B Week 28 N=606 n (%)
# of subjects with titers available	1804	1741	605	583
<1:160	1616 (89.3)	1662 (91.9)	541 (89.3)	554 (91.4)
≥1:160	188 (10.4)	79 (4.4)	64 (10.6)	29 (4.8)
1:160	115 (6.4)	41 (2.3)	39 (6.4)	13 (2.1)
1:320	50 (2.8)	19 (1.1)	17 (2.8)	13 (2.1)
1:640	14 (0.8)	11 (0.6)	2 (0.3)	1 (0.2)
1:1280	5 (0.3)	5 (0.3)	4 (0.7)	1 (0.2)
1:2560	2 (0.1)	2 (0.1)	1 (0.2)	0
1:5120	0	0	0	1 (0.2)
>1:5120	2 (0.1)	1 (0.1)	1 (0.2)	0

Source: *Adapted from STN 125428, DV2-HBV-10 Clinical Study Report Table 12-16, page 108*

Most subjects had ANA titers < 1:160 in both treatment groups at baseline and at week 28. The percentage of subjects with results within each serial dilution was comparable

between treatment groups. No trend towards increasing percentages of individuals with ANA titers ≥ 1:160 in the weeks subsequent to vaccination was noted among subjects receiving either Heplisav or Engerix-B.

Table 11 summarizes the changes in ANA titer from Week 0 to Week 28 by treatment group and antibody dilution. All subjects with titers that increased from baseline were ≥ 18 years old. The percentage of subjects experiencing an increase in ANA titer from baseline was similar between treatment groups.

Table 11: Summary of Change in ANA Titers from Baseline to Week 28 by Treatment Group (Study DV2-HBV-10)

Change from Baseline at Week 28	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)
1-dilution increase	31 (1.7)	8 (1.3)
2-dilution increase	10 (0.6)	6 (1.0)
3-dilution increase	1 (0.1)	0
4-dilution increase	0	0
>4-dilution increase	0	0
≥ 2-dilutiion increase	11 (0.6)	6 (1.0)
Any increase	53 (2.9)	20 (3.3)

Source: *Adapted from STN 125428, DV2-HBV-10 Clinical Study Report Table 12-16, page 108*

Only a small percentage of individuals were found to manifest an increase in ANA titers from baseline at 28 weeks following vaccination. No difference in the proportion of subjects developing increases in ANA titers was noted between Heplisav and Engerix-B recipients. Most subjects experiencing an increase in ANA titer had only a 1-dilution increase.

Anti-double stranded DNA Assessment

Anti-dsDNA was measured at Week 0 and Week 28. Table 12 summarizes the results by week and treatment group. In the HEPLISAV arm, more subjects had a positive result at Week 28 than at baseline (0.6% versus 0.3%). There was no change in the percentage of subjects with a positive result at Week 28 compared to baseline in the Engerix-B arm (0.5% at both time points).

Table 12: Summary of Anti-Double Stranded DNA by Visit and Treatment Group for Subjects ≥ 18 Years Old (Study DV2-HBV-10)

Result	HEPLISAV Baseline N=1809	HEPLISAV Week 28 N=1809	Engerix-B Baseline N=606	Engerix-B Week 28 N=606
# of Subjects with Anti-dsDNA data	1799	1740	602	583
Positive	6 (0.3)	10 (0.6)	3 (0.5)	3 (0.5)
Negative	1793 (99.1)	1730 (95.6)	599 (98.8)	580 (95.7)

Source: *STN 125428, Study DV2-HBV-10 CSR, Table 12-18, page 110*

Table 13 summarizes changes in result from baseline to Week 28. All subjects with changes in anti-dsDNA from baseline to Week 28 were ≥ 18 years old. There was no difference between groups in the percentage of subjects who had a negative result at baseline and a positive result at Week 28.

Table 13: Summary of Change in Anti-Double Stranded DNA from Baseline to Week 28 by Treatment Group for Subjects ≥ 18 Years Old (Study DV2-HBV-10)

Result	HEPLISAV N=1809	Engerix-B N=606
Negative to Negative	1716 (94.9)	573 (94.6)
Negative to Positive	9 (0.5)	3 (0.5)
Positive to Negative	5 (0.3)	3 (0.5)
Positive to Positive	0	0

Source: *STN 125428, Study DV2-HBV-10 CSR, Table 12-18, page 110*

Safety Summary: Review of the safety data revealed similar rates of local AEs, systemic AEs, SAEs, treatment related events, adverse events of special interest, and events leading to discontinuation from study in the Heplisav and Engerix-B study groups. Additionally, no clinically important differences in ANA titers or anti-dsDNA levels were seen between participants in the two vaccine arms.

Study Conclusion: Seroprotection rates following 2 doses of HEPLISAV were non-inferior to seroprotection rates after 3 doses of Engerix B. No clear safety concerns arose from the review of the safety database. Similar rates of adverse events were observed in both study groups. One case of c-ANCA-positive Wegener's granulomatosis occurred in a HEPLISAV recipient and one case of p-ANCA positive vasculitis occurred in an Engerix-B recipient who had pre-existing autoimmune disease. Independently, the development of Wegener's granulomatosis in temporal association with the receipt of HEPLISAV is notable. Additionally, the two cases of vasculitis in this study may not be comparable given that the subject in the Engerix-B arm had a history of autoimmune disease. However, the 3:1 randomization ratio, the single occurrence of this disease, and the 28 week follow-up period of this study make interpretation of the incidence of a rare disease difficult.

5.2 Study DV2-HBV-16

An observer-blinded, randomized, parallel-group, multi-center phase 3 study comparing the safety and immunogenicity of HEPLISAV to Licensed Vaccine (Engerix-B) among Healthy Adults 40 to 70 years of Age

5.2.1 Study Design

The study was a subject- and observer-blinded, randomized, controlled study of approximately 2000 adult subjects, 40 to 70 years of age. The study was conducted by 25 investigators at 29 sites in the U.S.A. and by 3 investigators at 3 sites in Canada. Initially, 400 subjects were randomized to receive one of the three consistency lots of HEPLISAV (TDG 008, TDG 009 or TDG 010), lot TDG006 (the lot prior to minor manufacturing process modifications) or Engerix-B at a 3:1:1 allocation ratio respectively. After reaching the subject enrollment target of 400 subjects for lot TDG006, 1200 subjects were randomized to receive one of the three consistency lots or Engerix-B at a 1:1:1:1 allocation ratio until enrollment was completed.

The overall allocation ratio of HEPLISAV, including lot TDG 006, to Engerix-B was 4:1. For the primary objective of noninferiority, the allocation ratio of the three consistency lots to Engerix-B was 3:1. For the primary objective of lot consistency, the allocation

ratio was 1:1:1. Randomization was stratified by age: 40 to 49 years, 50 to 59 years, and 60 to 70 years, and by study site.

Subjects randomized to Engerix-B received three injections of Engerix-B. Subjects randomized to HEPLISAV received two injections of HEPLISAV vaccine at Weeks 0 and 4 and saline placebo at Week 24. Thus, all subjects received a total of three injections (active vaccine or matching placebo), given on Day 0, Week 4 (1 month), and Week 24 (6 months). This dosing regimen and schedule was identical to that of the pivotal phase 3 study, DV2-HBV-10. Upon completion of Week 0, subjects returned to the clinical site at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 44, and 52 to undergo clinical safety evaluations and to have blood drawn for safety laboratory studies and anti-HBsAg serum concentrations. The duration of the study was 56 weeks.

5.2.2 Study Objectives

The co-primary immunogenicity objectives of this phase 3 study were: 1) to demonstrate lot consistency through clinical evaluation of three consecutively manufactured lots of HEPLISAV, and 2) to compare the proportion of subjects who exhibit a seroprotective immune response (SPR, defined as: antiHBs Ag antibody levels ≥ 10 mIU/mL) when measured at Week 12 following vaccination with HEPLISAV at 0 and 1 month to the proportion of subjects who exhibit SPRs when measured at Week 32 following vaccination with Engerix-B, at 0, 4, and 24 weeks. The primary safety objective of this study was to demonstrate safety and tolerability of vaccination with HEPLISAV when administered to subjects 40 to 70 years of age and to compare the safety profile to that of Engerix-B for this age group.

5.2.3 Study Population

The study enrolled HBV seronegative, low HBV-risk, male and female subjects 40-70 years of age who were serum negative for HBsAg, anti-HBsAg antibody and anti-HBcAg antibody and who have never received any prior HBV vaccine.

5.2.4 Endpoints and Criteria for Study Success

A summary table of immunogenicity testing and description of primary and secondary endpoints is presented in Table 14:

Table 14: Immunogenicity Testing (Study DV2-HBV-16)

Hypothesis	Study Parameter
Primary	Non-inferiority of SPR, measured at 8 weeks after the last active dose of HEPLISAV (combined lots) vs. Engerix-B
Primary	Lot-to-lot consistency measured by GMC at 4 weeks after last active dose among 3 consecutively manufactured HEPLISAV lots (008, 009, 010).
Secondary	Lot-to-lot consistency measured by SPR at 4 weeks after last active dose among 3 consecutively manufactured HEPLISAV lots (008, 009, 010).
Secondary	Bridging lot-to-lot consistency: measured by SPR and GMC at 4 weeks after last active dose among 3 consecutively manufactured HEPLISAV lots (008, 009, 010) and an older lot of HEPLISAV (006).

Source: *BLA 125428, DV2-HBV-16, Statistical Analysis Plan, 2. Study Objectives Page 8 of 38, Section 4.5. Immunogenicity Evaluation, pages 13-18 of 38*

For the primary immunogenicity endpoints—lot-to-lot consistency for the immune response as measured by the GMC at 4 weeks after the last active dose among three consecutively manufactured lots of HEPLISAV after minor modification in the manufacturing process—the GMC ratios between each pair of the three consistency lots were computed by a two-way Analysis of Variance (ANOVA) with the $\log_{10}$ of the anti-HBsAg concentration at each visit as the dependent variable and with factors for vaccine lot, study center and age category. Lot-to-lot consistency was established if all three CIs for the pairwise ratios of GMCs were embedded in the interval between 2/3 (0.667) and 1.5.

For the primary immunogenicity endpoint of 'comparison of the SPR between HEPLISAV and Engerix-B after the last dose of vaccine', the difference in SPRs between the combined three consistency lots of HEPLSAV and associated 95% CIs, eight weeks after the last respective dose of vaccine (Week 8 for HEPLISAV and Week 32 for Engerix-B, respectively) was evaluated. HEPLISAV was declared non-inferior to Engerix-B with respect to SPR if the lower limit of the 95% CIs of the difference in seroprotection rates (HEPLISAV seroprotection rate at Week 12 minus the Engerix-B seroprotection rate at Week 32) was greater than -10%.

5.2.5 Populations Analyzed

Three per protocol populations were used for the immunogenicity analysis in Study DV2-HBV-16, one for the noninferiority immunogenicity analysis, one for the lot consistency immunogenicity analysis, and one for the bridging study analysis (consistency of immune responses between lot TDG006 and the three combined consistency lots). These per protocol populations were defined as follows:

- Noninferiority Per Protocol Population: randomized subjects who received one of the three consistency lots of HEPLISAV or Engerix-B, received all three study injections as randomized and within the study visit windows, had no major protocol deviations, and had anti-HBsAg measurements and all injections within the specified day ranges (primary immunogenicity analysis population).

- Lot Consistency Per Protocol Population: all subjects randomized to one of three consistency lots of HEPLISAV who received the first two study injections within the study visit windows, had no major protocol deviations, and had anti-HBsAg levels obtained within study visit windows at baseline and Week 8.

- Bridging Study Per Protocol: all subjects randomized to lot TDG006 or to one of three consistency lots of HEPLISAV concurrently with lot TDG006 who received the first two study injections within the study visit windows, had no major protocol deviations and had anti-HBsAg levels obtained within study visit windows at baseline and Week 8.

5.2.6 Subject Disposition

A total of 2269 subjects (92.5% of the randomized population) completed the study and 183 subjects (7.5%) discontinued the study early (before Week 52). The percentage of subjects completing the study was similar across all treatment groups. The most common

reasons for early study discontinuation were lost to follow-up (3.8%), consent withdrawn (2.3%), and 'other' reasons (0.7%). Treatment compliance of the randomized population with the three-dose regimen remained high throughout the study. Compliance was similar across all treatment groups, with 94.3% of HEPLISAV consistency lot groups, 92.0% of the TDG006 group, and 94.4% of Engerix-B group subjects receiving all three doses of vaccine.

5.2.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics were similar between the two treatment groups. Within each group, almost all subjects were white or non-Hispanic/Latino, the mean age was approximately 40 years, and the percentage of females was slightly higher than that of males. The breakdown by age stratum was similar between the two treatment groups, with slightly more subjects in the 40 through 55 year subgroup (991 and 331 subjects, respectively for HEPLISAV vs. Engerix-B) than the 18 through 39 year subgroup (818 and 275, respectively, HEPLISAV vs. Engerix-B). More than 99% of subjects in each treatment group had an anti-HBsAg level below 5 mIU/mL at baseline. The majority of enrolled study subjects (63-64% for both treatment groups) were non-smokers.

5.2.8 Immunogenicity Results

Primary Immunogenicity Endpoints

Immunogenicity criteria for demonstration of lot consistency were met when measured 8 weeks after the last vaccination of HEPLISAV (Week 12). Accordingly, CBER determined that clinical consistency of the three consecutively manufactured lots of HEPLISAV was demonstrated (data not shown).

For the comparison of SPRs at 8 weeks after the last active dose of study treatment between HEPLISAV (Week 12) and Engerix-B (Week 32) for the per protocol population, noninferiority was demonstrated between the two treatment arms (Table 15). The SPR in the HEPLISAV group was 90.0% and that of the Engerix-B group was 70.5%; the estimated difference between these rates was 19.6% (HEPLISAV- Engerix-B; 95% CI 14.7%, 24.7%). Because the lower limit of the 95% CI (14.7%) was greater than -10%, the SPR for the HEPLISAV group at Week 12 met the pre-specified non-inferiority SPR criterion for the Engerix-B group at Week 32.

Table 15: Primary Immunogenicity Endpoint Analysis: SPR for HEPLISAV (Week 12) compared with Engerix-B (Week 32): Per-Protocol Analysis Population, Adults 40-70 Years of Age (Study DV2-HBV-16)

Visit	HEPLISAV[a] SPR (%) (n/N)	Engerix-B[b] SPR (%) (n/N)	Estimated Difference in SPR[c] (HEPLISAV-Engerix-B (95%) CI)	Non-inferiority Criteria Met?[d] (Yes/No)
8 Weeks after last dose	90.0 % (Week 12) (1011/1123)	70.5 % (Week 32) (253/359)	19.6% (14.7%, 24.7%)	Yes

CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.
[a] Study injections were given at Weeks 0, 4, 24 (placebo). [b] Study injections were given at Weeks 0, 4, 24.
[c] Two-sided 95% CIs of the difference in seroprotection rates between the HEPLISAV group at 12 weeks and the Engerix-B group at 32 weeks was computed using the Newcombe score method with continuity correction.
[d] Non-inferiority was supported if the lower limit of the two-sided 95% CI was greater than -10%.
Source: *BLA STN 125428, Clinical Study Report, DV2-HBV-16, Table 11-1, Page 83 of 215*

Exploratory Analyses

Exploratory analyses comprised a comparison of SPR and GMCs, for HEPLISAV and Engerix-B vaccinated subjects at each study visit are presented because of their relevance to assessing the kinetics of the immune response and the duration of effect of HEPLISAV, in the context of a 52-week long trial. Table 16 summarizes the comparisons of the estimated SPRs for each time point.

Table 16: Comparison of Seroprotection Rates Between HEPLISAV and Engerix-B by Visit: Per-Protocol Analysis Population; Adults 40-70 Years of Age (Study DV2-HBV-16)

Visit	n/N	HEPLISAV[a] SPR (95 %CI)[c]	n/N	Engerix-B[b] SPR (95% CI)[c]	% Difference in SPR[d] (HEPLISAV-Engerix-B (95% CI)
Week 4	223/1123	19.9% (17.6%, 22.3%)	16/359	4.5% (2.6%, 7.1%)	15.4% (11.9%, 18.4%)
Week 8	859/1122	76.6% (74.0%, 79.0%)	73/359	20.3% (16.3%, 24.9%)	56.2% (51.1%, 60.7%)
Week 12	1011/1123	90.0% (88.1%, 91.7%)	61/359	17.0% (13.3%, 21.3%)	73.0% (68.4%, 76.9%)
Week 18	1062/1123	94.6% (93.1%, 95.8%)	70/359	19.5% (15.5%, 24.0%)	75.1% (70.4%, 79.0%)
Week 24	1068/1123	95.1% (93.7%, 96.3%)	77/359	21.4% (17.3%, 26.1%)	73.7% (68.9%, 77.7%)
Week 28	1064/1122	94.8% (93.4%, 96.1%)	260/357	72.8% (67.9%, 77.4%)	22.0% (17.4%, 27.0%)
Week 32	1065/1123	94.8% (93.4%, 96.1%)	253/359	70.5% (65.5%, 75.1%)	24.4% (19.7%, 29.4%)
Week 36	1048/1111	94.3% (92.8%, 95.6%)	233/355	65.5% (60.4%, 70.6%)	28.7% (23.7%, 33.9%)
Week 44	1030/1103	93.4% (91.8%, 94.8%)	211/353	59.8% (54.5%, 64.9%)	33.6% (28.4%, 39.0%)
Week 52	1012/1101	91.9% (90.1%, 93.5%)	209/354	59.0% (53.7%, 64.2%)	32.9% (27.6%, 38.3%)

CI = Confidence interval, N = number of subjects in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL. [a] Study injections were given at Weeks 0, 4, 24 (placebo).[b] Study injections were given at Weeks 0, 4, 24. [c] Calculated using the Clopper Pearson method. [d] Two-sided 95% CI of the % difference in proportions between the HEPLISAV and Engerix-B group at each visit were computed using the Newcombe score method with continuity correction.
Source: *BLA STN 125428, DV2-HBV-16, Clinical Study Report, Table 11-7, page 93 of 215*

A similar trend in immune response was seen with analysis of the GMCs by study visit for HEPLISAV vs. Engerix-B (Table 17).

Table 17: Comparison of Anti-HBsAg Geometric Mean Concentration (mIU/mL) Between HEPLISAV and Engerix-B by Study Visit: Per-Protocol Analysis Population; Adults 40-70 Years of Age (Study DV2-HBV-16)

Visit	N	HEPLISAV[a] GMC (95 %CI)	N	Engerix-B[b] GMC (95% CI)	Ratio HEPLISAV/Engerix-B (95% CI)
Week 4	1123	1.3 (1.1, 1.6)	359	0.2 (0.2, 0.3)	5.75 (4.20, 7.69)
Week 8	1122	41.5 (36.1, 47.6)	359	0.9 (0.7, 1.2)	44.23 (33.04, 59.20)
Week 12	1123	93.0 (82.9, 104.2)	359	0.8 (0.6, 1.1)	113.35 (88.35, 145, 42)
Week 18	1123	192.2 (173.8, 212.6)	359	0.9 (0.7, 1.1)	220.44 (175.36, 277.12)
Week 24	1123	232.7 (210.2, 257.5)	359	1.0 (0.8, 1.3)	137.67 (188.80, 299.18)
Week 28	1122	232.0 (209.2, 257.2)	356	88.5 (59.4, 131.9)	2.62 (1.96, 3.50)
Week 32	1123	222.3 (200.3, 246.7)	359	61.4 (41.7, 90.5)	3.62 (2.72, 4.82)
Week 36	1111	208.6 (187.6, 231.9)	355	46.8 (31.8, 68.8)	4.46 (3.35, 5.94)
Week 44	1103	180.1 (161.9, 200.5)	353	27.2 (18.7, 39.6)	6.62 (4.99, 8.79)
Week 52	1101	150.7 (134.8, 168.5)	354	19.5 (13.5, 28.1)	7.74 (5.82, 10.30)

GMC= geometric mean concentration, N = number of subjects in the analysis population in the treatment group.
[a] Study injections were given at Weeks 0, 4, 24 (placebo). [b] Study injections were given at Weeks 0, 4, 24.
Source: *BLA STN 125428, DV2-HBV-16, Clinical Study Report, Table 11-9, page 98 of 215*

The GMCs for the HEPLISAV vaccinated subjects peaked at week 24 and remained elevated relative to the Engerix B vaccinated subjects through week 52.

5.2.9 Safety results

Safety monitoring for Study DV2-HBV-16 was conducted in a similar manner as in Study DV2-HBV-10, with the exception that an algorithm was prospectively designed to capture autoimmune adverse events of special interest (AESIs). The safety population consisted of all subjects who received at least one study injection, excluding subjects who had no on-study safety data. The safety population included 2449 subjects (lot TDG008: n=481; lot TDG009: n=481; lot TDG010: n=477; lot TDG006: n=529; Engerix-B: n=481).

The reporting period for non-serious AEs was the time period from the first injection (Week 0) until 4 weeks after the third injection (Week 28). Overall, the proportions of subjects experiencing any AE were similar among treatment groups. There were more active injections in the Engerix-B group and therefore more AEs reported after active injections in this treatment arm than in other arms. The reporting period for SAEs and AIAEs was from the first injection (Week 0) to 28 weeks after the third injection (Week 52). There were 7 (0.5%) investigator-reported AIAEs among the HEPLISAV consistency lots, but none in Lot TDG006 or Engerix-B arms. SAEs occurred with similar frequency among treatment groups; the SAE rate among subjects vaccinated with HEPLISAV consistency lots was 3.4%. More AEs led to discontinuation of treatment in the HEPLISAV lots (consistency lots total: 0.9%, Lot TDG006: 0.8%) than in the Engerix-B arm (0.4%).

Solicited adverse events:

Solicited adverse events included local pain, redness and swelling, fatigue, headache, malaise, myalgia, and elevated oral temperature (Tables 18 and 19). More subjects receiving HEPLISAV reported injection site redness and pain than did subjects receiving Engerix-B, though the majority of reactions were mild in intensity. The incidence and severity of malaise, headache, myalgia, and fatigue were similar among treatment groups for both active doses. The vast majority of subjects did not report fever after vaccination,

and fever intensity was similar among treatment groups. Most solicited systemic adverse events were graded as mild or moderate in intensity.

Table 18: Summary of Solicited Local Adverse Reactions (Days 0-6) by Active Injection and Treatment Group (Study DV2-HBV-16)

	HEPLISAV Consistency Lot TDG008 N=481	HEPLISAV Consistency Lot TDG009 N=481	HEPLISAV Consistency Lot TDG010 N=477	All HEPLISAV Consistency Lots N=1439	HEPLISAV Lot TDG006 N=529	Engerix-B N=481
Dose 1						
n	475	479	473	1427	525	477
Redness, n (%)	77 (16.2)	79 (16.5)	88 (18.6)	244 (17.1)	103 (19.6)	72 (15.1)
Swelling, n (%)	40 (8.4)	37 (7.7)	46 (9.7)	123 (8.6)	49 (9.3)	38 (8.0)
Pain, n (%)	96 (20.2)	102 (21.3)	121 (25.6)	319 (22.4)	143 (27.2)	88 (18.4)
Dose 2						
n	467	469	462	1398	507	464
Redness, n (%)	49 (10.5)	53 (11.3)	48 (10.4)	150 (10.7)	84 (16.6)	45 (9.7)
Swelling, n (%)	27 (5.8)	30 (6.4)	30 (6.5)	87 (6.2)	37 (7.3)	26 (5.6)
Pain, n (%)	103 (22.1)	102 (21.7)	109 (23.6)	314 (22.5)	120 (23.7)	74 (15.9)

Source: *Adapted from STN 125428, DV2-HBV-16 Main Study Report Table 14.1.4-4, pp. 8-16*

Table 19: Summary of Solicited Systemic Adverse Events (Days 0-6) by Injection and Treatment Group (Study DV2-HBV-16)

	HEPLISAV Consistency Lot TDG008 N=481	HEPLISAV Consistency Lot TDG009 N=481	HEPLISAV Consistency Lot TDG010 N=477	All HEPLISAV Consistency Lots N=1439	HEPLISAV Lot TDG006 N=529	Engerix-B N=481
Dose 1						
n	475	479	473	1427	525	477
Malaise, n (%)	36 (7.6)	32 (6.7)	40 (8.5)	108 (7.6)	43 (8.2)	41 (8.6)
Headache, n (%)	58 (12.2)	47 (9.8)	64 (13.5)	169 (11.8)	61 (11.6)	57 (11.9)
Myalgia, n (%)	40 (8.4)	36 (7.5)	40 (8.5)	116 (8.1)	50 (9.5)	46 (9.6)
Fatigue, n (%)	63 (13.3)	53 (11.1)	62 (13.1)	178 (12.5)	68 (13.0)	61 (12.8)
Dose 2						
n	467	469	462	1398	507	464
Malaise, n (%)	33 (7.1)	30 (6.4)	29 (6.3)	92 (6.6)	42 (8.3)	33 (7.1)
Headache, n (%)	35 (7.5)	38 (8.1)	41 (8.9)	114 (8.2)	41 (8.1)	44 (9.5)
Myalgia, n (%)	23 (4.9)	27 (5.8)	30 (6.5)	80 (5.7)	42 (8.3)	37 (8.0)
Fatigue, n (%)	44 (9.4)	50 (10.7)	53 (11.5)	147 (10.5)	58 (11.4)	56 (12.1)

Source: *Adapted from STN 125428, DV2-HBV-16 Main Study Report Table 14.1.4-4, pp. 8-16*

Unsolicited Adverse Events:

Adverse events rated as grade 3 or higher occurred with a slightly lower incidence in the HEPLISAV consistency lots (4.5%) than in Lot TDG006 (5.9%) or the Engerix-B arm (5.8%).

The majority of unsolicited adverse were deemed unrelated to the study vaccine by the investigator. The unsolicited adverse events most frequently reported among HEPLISAV recipients are presented in Table 20.

Table 20: Unsolicited Adverse Events most Frequently Reported among HEPLISAV Recipients (Study DV2-HBV-16)

Adverse Event	HEPLISAV Consistency Lots (%)	HEPLISAV Lot TDG006 (%)	Engerix-B (%)
Nasopharyngitis	4.0	4.2	5.2
Upper respiratory infection	3.8	2.8	4.0
Arthalgia	2.8	2.5	2.9
Sinusitis	2.8	1.9	2.9
Pain in extremity	2.1	2.5	1.0
Back pain	1.9	1.5	1.9
Cough	1.7	1.3	1.7
Diarrhea	1.7	1.3	1.7
Rash	1.7	0.9	1.7
Osteoarthritis	1.5	0.8	2.9
Musculoskeletal pain	1.3	1.3	1.7
Nausea	1.0	1.5	0.8
Hypertension	1.0	1.7	2.9

Source: *Adapted from STN 125428, DV2-HBV-16 Main Study Report: Table 14.1.4-15, pages 114-133*

Solicited adverse events that persisted or worsened past Day 7 were recorded as AEs are presented in Table 21.

Table 21: Solicited Adverse Events that Persisted or Worsened Past Day 7 (Study DV2-HBV-16)

Adverse Event	HEPLISAV Consistency Lots (%)	HEPLISAV Lot TDG006 (%)	Engerix-B (%)
Headache	3.1	2.3	2.9
Myalgia	1.9	1.1	2.9
Injection site erythema	1.5	1.3	0.8
Fatigue	1.3	2.1	2.3
Malaise	0.6	0.4	1.5

Source: *Adapted from STN 125428, DV2-HBV-16 Main Study Report: Table 14.1.4-15, pages 114-133*

Deaths

Two deaths were reported in study DV2-HBV-16, one in a HEPLISAV recipient and one in an Engerix-B recipient:

1. A report of pulmonary embolus which occurred 46 days after the second study injection of HEPLISAV, in a 46 year old active white male with no relevant past medical history; including no history of a coagulation disorder, preceding trauma, or other pre-disposing cause for hypercoagulability (Subject 22-003). The investigator assessed the event as not related to study treatment, but no autopsy information was available on this subject.

2. A report of fatal myocardial infarction in a 64 year old black or African American male with a history of gout, hypertension, gastroesophageal reflux and bilateral knee osteoarthritis (Subject 92-638) which occurred 43 days after the second study injection of Engerix-B. The investigator assessed the cardiac arrest as not related to the study treatment.

Non-fatal SAEs occurred with similar frequency in the HEPLISAV consistency lots and the Engerix-B group. Forty-nine subjects (3.4%) in the HEPLISAV consistency lots experienced 62 SAEs, 27 (5.1%) subjects in the lot TDG006 group experienced 28 SAEs,

and 23 (4.8%) subjects receiving Engerix-B experienced 30 SAEs. Overall, the most common organ systems represented by SAEs were musculoskeletal and connective tissue disorders (HEPLISAV consistency lots: 1.1%, TDG006 0.6%, Engerix-B 1.0%), injury, poisoning and procedural disorders (HEPLISAV consistency lots: 0.8%, TDG006: 0.4%, Engerix-B 0.6%), neoplasms (HEPLISAV consistency lots: 0.6%, TDG006: 0.2%, Engerix-B 1.0%) and cardiac disorders (HEPLISAV consistency lots: 0.2%, TDG006 0.8%, Engerix-B 0.8%).

Autoimmune Adverse Events

Nine potential autoimmune adverse events were reported: hypothyroidism (n=5), Bell's palsy (n=1), erythema nodosum (n=1), vitiligo (n=1) and microscopic colitis (n=1). Seven of these events were confirmed by expert evaluation to be potentially autoimmune in nature: hypothyroidism (n=4), Bell's palsy (n=1), erythema nodosum (n=1), and vitiligo (n=1). All of these events occurred in subjects in the HEPLISAV consistency lot group (7/1439, 0.5%), were mild to moderate in severity, and were considered nonserious.

Per protocol, these potential new-onset AIAEs were referred to the Safety Evaluation and Adjudication Committee (SEAC) for adjudication. Five of these 7 events were initially confirmed by the SEAC as new-onset autoimmune events: hypothyroidism (n=4) and vitiligo (n=1). Of the 4 initially confirmed events of hypothyroidism, post-study testing of banked baseline serum from two of these subjects revealed a high thyroid stimulating hormone (TSH) level and low free T4 level, providing laboratory evidence of pre-existing hypothyroidism, and they were therefore not new onset events. Upon revision of adjudications, three cases of SEAC-confirmed new-onset AIAEs were determined to have occurred: hypothyroidism (n=2) and vitiligo (n=1).

Antinuclear Antibody Evaluation

Blood samples for ANA and anti-dsDNA determination were obtained at Weeks 0 and 52, or at the point of early discontinuation. Table 22 compares the baseline ANA status and change from baseline ANA status among treatment groups. The majority of subjects had a negative ANA, defined as <1:160. Positive ANA values were stratified by serial dilution. The distribution of titers within each serial dilution was similar between treatment groups. The change in the percentage of subjects with positive ANA values from baseline to Week 52 was 6.5% in the HEPLISAV consistency lots total group, 11.2% in the lot TDG006 group and 7.4% in the Engerix-B group.

Table 22: Antinuclear Antibody Titers by Treatment Group and Visit (Study DV2-HBV-16)

Result	HEPLISAV Consistency Lots Baseline N=1439 n (%)	HEPLISAV Consistency Lots Week 52 N=1439 n (%)	Lot TDG006 Baseline N=529 n (%)	Lot TDG006 Week 52 N=529 n (%)	Engerix-B Baseline N=481 n (%)	Engerix-B Week 52 N=481 n (%)
Number of subjects with titers available	1439	1356	529	486	480	455
<1:160	1375 (95.6)	1208 (89.1)	499 (94.3)	404 (83.1)	447 (93.1)	390 (85.7)
≥1:160	64 (4.4)	148 (10.9)	30 (5.7)	82 (16.9)	33 (6.9)	65 (14.3)
1:160	29 (2.0)	96 (7.1)	14 (2.6)	49 (10.1)	22 (4.6)	37 (8.1)
1:320	22 (1.5)	35 (2.6)	11 (2.1)	18 (3.7)	8 (1.7)	16 (3.5)
1:640	8 (0.6)	12 (0.9)	3 (0.6)	7 (1.4)	2 (0.4)	7 (1.5)
1:1280	5 (0.3)	4 (0.3)	2 (0.4)	6 (1.2)	1 (0.2)	5 (1.1)
1:2560	0	1 (0.1)	0	2 (0.4)	0	0
>1:2560	0	0	0	0	0	0

Source: *Adapted from STN 125428, DV2-HBV-16 Main Study Report; Table 12-19, page 185*

The majority of subjects had normal ANA titers after vaccination. The distribution of serial dilutions was similar between groups. A descriptive analysis showed that more subjects receiving lot TDG006, an older lot used in early studies, converted to positive ANA status than did the other groups. The percentage of subjects with positive titers increased by a similar amount in the HEPLISAV consistency lots and the Engerix-B group, respectively, at Week 52. Therefore, the ANA evaluation did not raise clinical concerns.

The majority of subjects in each arm had negative ANA titers at baseline. A comparable proportion of subjects in each arm converted from a negative baseline titer to a positive titer at Week 52 (data not shown). Change in ANA status was similar between the study vaccine and the active comparator and therefore raises no clinical concerns.

Anti-dsDNA Evaluation

Table 23 summarizes the results of the anti-dsDNA evaluation by treatment group. The majority of subjects had negative results at baseline and Week 52. A similar proportion of subjects converted from a negative to a positive result by Week 52, with the exception of Lot TDG009 which had the lowest number of subjects convert to positive.

Table 23: Anti-dsDNA Antibody Results at Baseline and Week 52 by Treatment Group (Study DV2-HBV-16)

Result	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots N=1439	Lot TDG006 N=529	Engerix-B N=481
Negative anti-dsDNA Week 0	476/481 (99.0%)	471/481 (97.9%)	470/477 (98.5%)	1417/1439 (98.5%)	519/529 (98.1%)	467/480 (97.3%)
Negative anti-dsDNA Week 52	445/455 (97.8%)	441/450 (98.0%)	439/451 (97.3%)	1325/1356 (97.7%)	469/485 (96.7%)	439/455 (96.5%)
Negative at Week 0, Positive at Week 52	10/450 (2.2%)	4/442 (0.9%)	10/446 (2.2%)	24/1338 (1.8%)	12/465 (2.5%)	7/434 (1.6%)
Positive at Week 0, Negative at Week 52	0/5 (0.0%)	5/8 (62.5%)	2/5 (40.0%)	7/18 (39.9%)	4/8 (50.0%)	9/13 (69.2%)

Source: *STN 125428, Study DV2-HBV-16 Clinical Study Report, Table 12-20, page 186*

The proportion of subjects converting from a negative to a positive result by Week 52 was comparable between recipients of Heplisav and Engerix-B. A small number of subjects with positive results at baseline had negative results at Week 52. The clinical significance of this change is unclear. No safety signals were found upon review of the anti-dsDNA data.

The incidence of adverse events was analyzed by ANA and anti-dsDNA status. Overall, there did not appear to be a significant increase in the occurrence of AEs among those with a positive ANA or anti-dsDNA at Week 52.

Study Conclusion: Immunogenicity data supporting lot consistency was shown, and HEPLISAV was non-inferior to Engerix B with respect to seroprotection rates in this second pivotal study. The overall rates of solicited and unsolicited AEs, SAEs and AESIs were similar among the consistency lots, the older manufacturing lot TDG006, and Engerix-B. No significant differences in ANA titers or anti-dsDNA levels were seen among the different treatment arms. While the incidence of autoimmune events was low, all autoimmune AEs occurred in HEPLISAV recipients. Given the randomization ratio employed in this study and the low background incidence of many autoimmune diseases, the clinical significance of the 0.5% difference in the incidence of potential autoimmune disease between groups is unclear. Due to the reports of thyroid disorders, an independent CBER analysis revealed that thyroid related AEs were reported by HEPLISAV recipients with a frequency similar to that of Engerix-B recipients and the background incidence rate across all studies. As the numerical differences in the incidence of these AIAEs in this study did not persist upon integrated analysis of all studies, CBER determined that study DV2-HBV-16 did not reveal clinically significant safety concerns. However, it is acknowledged that the ability to reliably evaluate uncommon specific autoimmune events is limited due to the size of the study.

6.0 Integrated Summary of Safety: Key Points

6.1 Demographic Data

In the Integrated Summary of Safety, the safety population included subjects who received at least 1 dose of HEPLISAV or Engerix-B and had any post-baseline safety assessment (N = 5845).

More females than males received both HEPLISAV (52.4% females) and Engerix-B (54.3% females). Most subjects were age 40-55, of white race, and non-Hispanic ethnicity. The demographic characteristics of subjects receiving HEPLISAV and Engerix-B do not suggest that selection bias based on age, sex, race or Hispanic ethnicity was introduced. Weight, height, BMI and smoking status also were similar between groups.

6.2 Adverse Events

6.2.1 Deaths

There were two deaths in study DV2-HBV-16 (Section 5.2.6). There were no deaths in other studies.

6.2.2 Nonfatal Serious Adverse Events (SAEs)

Treatment emergent SAEs were assessed for all subjects 18-70 years of age. None of the 13 subjects aged 11-17 years reported SAEs. The proportion of subjects with any SAE was similar between treatment groups for all tiers (range 2.7% to 3.7%). Overall, the incidence of SAEs was similar between treatment groups and did not raise safety concerns.

6.2.3 ANA Results

ANA testing was performed as a protocol-specified assessment in all trials except DV2-HBV-04. ANA results from HBV0001 were excluded from analysis because they were not reported as titers. These data confirm the data from the two pivotal studies previously presented and demonstrate that there does not appear to be an increased risk of converting from an ANA titer of <1:160 to a higher titer for HEPLISAV recipients as compared to Engerix-B recipients.

6.2.4 Anti-dsDNA Assessment

Anti-dsDNA testing was performed as a protocol-specified assessment in all trials except DV2-HBV-04 and DV2-HBV-08. The majority of subjects maintained a negative anti-dsDNA test throughout their participation in the study in which they were enrolled. As was seen in the two pivotal studies, a similar and small proportion of HEPLISAV and Engerix-B recipients had negative anti-dsDNA results at baseline and positive results post-treatment.

6.2.5. Anti-Neutrophil Cytoplasmic Antibody (ANCA) Assessment

Assessments for ANCA were described in association with Study DV2-HBV-10 and Study DV2-HBV-14 (see sections 5.1.6 and 5.2.6, above). In summary, subset analysis of serum ANCA results, as well as AE and SAE analyses, indicate that there does not appear to be an increased risk of developing ANCA-associated vasculitides among recipients of HEPLISAV over that of recipients of the licensed comparator.

Integrated Summary of Safety Conclusion: Review of the local and systemic reactogenicity data, unsolicited AE and SAE data, and testing for ANA, anti-dsDNA, and c-ANCA, did not detect clinically relevant differences in safety outcomes among HEPLISAV-immunized subjects, when compared to Engerix-B-immunized subjects.

7.0 Pharmacovigilance Plan

Dynavax has proposed an open-label, prospective, observational study to assess the incidence of medically significant adverse events, including autoimmune disease, in 5000 individuals initiating vaccination with HEPLISAV. A concurrent population of 5000 individuals initiating vaccination with Engerix-B will be evaluated for comparison. Participants will be followed for 12 months after the first injection. In addition to this postmarketing study, Dynavax has proposed routine pharmacovigilance to identify potential risks.

Safety was evaluated in 5845 adults enrolled in nine clinical trials: 2 pivotal studies, DV2-HBV-10 and DV2-HBV-16, and 7 supportive studies. No significant differences in safety profiles were demonstrated between HEPLISAV (n= 4425) and its active comparator (n= 1420). Review of the local and systemic reactogenicity data, solicited and unsolicited AE data; and testing for ANA, anti-dsDNA, and c-ANCA did not detect a clinically relevant safety signal in HEPLISAV-immunized subjects, when compared to Engerix-B. Most AEs were related to local and systemic reactogenicity and were mild in intensity. There did not appear to be a difference in the potential for autoimmunity between HEPLISAV and a non-adjuvanted hepatitis B vaccine comparator. However, given the relatively low incidence of many autoimmune diseases in the general population, the often non-specific initial presentation of these diseases and the limitations imposed by follow up periods, the pre-licensure safety database for this vaccine with a new adjuvant may not have sufficient power to detect rare adverse events, Additionally, the safety database for this new adjuvant is limited to the studies conducted using this product. For all of these reasons, CBER recommends further post-marketing evaluation of this product in a larger population of individuals.

8.0 VRBPAC Meeting

The questions to the Committee will focus on the adequacy of the safety and effectiveness data to support licensure of HEPLISAV for the proposed indication of active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age.

9.0 References

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